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Molecular Studies of Type 2 Diabetes in Reference of Antidiabetes Drugs

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Abstract – Diabetes is increasingly growing in India as a possible epidemic with > 62 million diagnosed people. In relation to the possible burden of diabetes on India, India is currently facing an uncertain future. A projected US €2.2 billion is required for all Type 2 diabetes mellitus (T2DM) cases in India to be adequately handled. The burden of this disease can be minimised with several acts. However, the resources of healthcare are minimal, so diabetes treatment measures should be given priority. The current research tests the economic efficacy of antidiabetic drugs in Mumbai, India patients with T2DM. The cost-effectiveness of antidiabetic treatment in T2DM patients has been investigated in a forward-looking cross-sectional analysis. A total of 152 patients with T2DM from F-Northward, Mumbai , India, were interviewed face-to - face with a validated questionnaire. Efficacy based on costs, efficacy, adverse drug reactions, safety of administration, frequency of administering, and bioavailability have been calculated. Cost-effectiveness for non-obese participants.

Key Words – Type 2 Diabetes Mellitus, Antidiabetic Drugs, Cost-Effectiveness

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INTRODUCTION

In the last decades, the diabetic patients have alarmingly increased, particularly due to the increased rates of T2DM. Besides the health problems, this is associated with severe economic and sociologic problems. Diabetic patients are treated at high cost and the amount of money spent annually is increased. A variety of antidiabetic medications may be utilized on the market, either for monotherapy or in combination. Each compound's action mechanisms are different & can be different, including doses, depending on various conditions. The antidiabetic medicines are designed to regulate the metabolism of glucose, & we may claim in a non-specialist approach that the target of gold is to lower blood glucose levels.

The bulk of its action mechanisms are also closely related to the metabolism of glucose. Unfortunately, most of these compounds compensate loss of insulin sensitivity, of insulin action or of insulin secretion, as well as other mechanisms responsible for the disease, but are unable to avoid or treat some of the deleterious effects. In addition, this is a field of research in constant change with the development of new products and intense research. DM is a multifactorial disease, demonstrating that the search for new objectives for this disease or for the mode of action of compounds with possible antidiabetic activity involves complex study. Diabetes prevalence and incidence rates in India are increasing rapidly, along with the high economic burden of its complications. The estimated US$ 2,2 billion will be required to deal adequately with T2DM cases in India.10 In India the future burden of diabetes on the country is currently unknown. It is very important to conduct studies focusing on economic evaluations to make evidence based health decisions and, consequently, to offer the best risk and cost-effective treatment choices along with better quality of life for patients with diabetes. This research was planned to test the efficacy of antidiabetic drugs in Mumbai-India T2DM patients.

DIABETES MELLITUS IN BRIEF

DM is chronic conditions in developed & developing countries, & leading cause of morbidity and mortality. It is stated that DM is available at 382 million, and by 2035, the number of diabetic patients is anticipated to rise 592 million. This pathology & its implications for cells , organs & whole body are therefore strongly encouraged. DM is identified as a group of chronic metabolic disordants characterized by insulin defects, insulin secretion or both. DM is classified as metabolic disorders. This deficiency leads to disturbances in the metabolism of carbohydrates, fat and protein, which causes systemic complications and co-morbidities namely cardiovascular and renal failure. The most predominant types of DM are T1DM & T2DM. T1DM is a chronic autoimmune

disease caused by the pathogenic action of T lymphocytes on insulin-producing **α** -cells. This leads to a dramatic reduction or even elimination of insulin production. Typically, the symptoms of T1DM appear in patients with less than 30 years, being known as juvenile-onset diabetes. The incidence of T1DM has been growing globally & it is estimated that new European children under 5 years of age would double from 2005 to 2020, if this trend persists. In contrast, the prevalence of cases in people under the age of 15 is projected to increase by 70% in this time. T2DM is characterised by insulin-resistant and inadequate insulin secretion. T2DM is known as hyperglycemia. While the triggering pathogenic elements tend to be new lifestyles in modern cultures, genetic factors have also shown to be part of T2DM pathogensis.

ANTIDIABETIC DRUGS

Inhibitors of α-Glucosidases

Core ingredients in western diets are carbon hydrates. In the effects of α-galactosidases, α-amylase & α-glucosidoses, complex carbohydrates are enzymatically reduced to monosaccharides. Thus, inhibitors of intestinal **α** -glucosidase enzymes modulate the rate of digestion of complex carbohydrates and disaccharides by competitively and reversibly inhibiting **α** - glucosidases. Importantly, it presents some adverse effects. The most common are flatulence, diarrhoea, and abdominal discomfort caused by altered bacterial metabolism of disaccharides in the colon. Several of the drawbacks include insignificant cholesterol effect and possible rise in liver liver enzymes. Currently, three inhibitors of α-glucosidase used as antidiabetic medicines are available: acarbose; miglitol; & voglibose. Miglitol has been licenced & voglibose is only available in Japan, whereas acarbose is easily obtainable.

Miglitol has a formation very much like glucose & first inhibitor of pseudomonosaccharides α-glucosidesase, derived from 1-deoxynojirimycin. In the upper portion of the small intestine, it is nearly entirely absorbed, has poor tissue penetration & excreted unchanged in the renals, as compared to acarboid. It is mostly effective against sucrose, inhibiting also glucoamylase, isomaltase, lactase and trehalase. The normal administration of miglitol is usually 50 mg though it may be enlarged to 100 mg 3 times per day after a few weeks, which is the maximal recommended daily dosage.

Voglibose is a valiolamine derivative, which is produced by *Streptomyces Hygroscopicus*. Similarly to acarbose, voglibose is slowly & poorly absorbed, being rapidly excreted. Like the other **α** -glucosidases inhibitors, voglibose also stimulates an increase of endogenous glucagon-like peptide-1 (GLP-1), an incretin hormone with antihyperglycemic properties.

Biguanides

Several glucose-lowering guanidine derivatives were introduced in the 1920s, due to the finding that *Galega officinalis*, a traditional herb historically used as treatment for DM, was rich in guanidine. These agents were almost forgotten as insulin became widely available and used. In the late 1950s, three biguanides with antidiabetic action were reported: phenformin, buformin and metformin. The use of phenformin and buformin has been discontinued in many countries due to a high incidence of lactic acidosis, leaving metformin as the main biguanide used worldwide. Metformin was in fact utilized for more than 50 years for T2DM therapy. The first-line treatment for this condition is typically identified with diet & exercise. Metformin is a medicine which makes an insulin sensitive & has its antifouling impact by blocking liver gluconeogenes, instead of directly inhibiting the expression of the gluconeogenic gene.

Sulfonylureas

An incidental observation of hypoglycemia episodes during treatment with sulfonamides in the 1940s, led to the concept and development of sulfonylureas as agents to stimulate insulin secretion. By 1955, sulfonylureas became the first pharmacological option to treat non-insulin-dependent DM, besides insulin injections. The first sulfonylureas developed were tolbutamide, chlorpropamide, acetohexamide and to lazamide. These first generation agents have been largely set aside by the newer second generation agents gliclazide, glipizide and glibenclamide (glyburide).

METHODS

Design & Participants

A prospective, randomized, cross sectional study was designed based on validated survey questionnaire. It was conducted in F-North ward of Mumbai, Maharashtra, India. V.V. gained ethical approval. Independent Hospital Board on Ethics, Thane, India. The analysis was carried out between 1 February 2016 and 30 April 2016. The F-North Ward office, Mumbai Municipal Corporation, collected details on apartments & family members. 1000 apartments were chosen randomly from their database of subjects between the ages of 30 & 75. Educated pharmacy students visited these flats & total of 200 participants who met the inclusion requirements, 166 of whom decided to take part. The inclusion criteria were age of 18–65 years, T2D diagnosed within the 2 years prior to initiation of the present study, a consultation and a diabetes report from a physician within the period of 30 days prior to the interview date and written informed consent to

participation in the study. Exclusion criteria were subjects with serious illness or pregnancy.

Study instrument

A survey questionnaire was designed in English after discussion with experts and a literature review of similar studies. In order to ensure that the content was compatible with another professional translator, the questionnaire was translated into the local & marathi languages. In pilot studies of a subsample of 30 individuals, the validity of the questionnaire was tested to ensure that the questionnaire was suitable & understandable among potential respondents. The pilot tests permitted wording changes to questions & calculated the average interview time & questionnaire completion time. Population were not included in the final report.

Collection of data

Each selected apartment was trained pharmacy student to collect the data. The purpose of the research was explained to the participant. Anonymity and confidentiality were guaranteed and maintained. The researchers complied with the international ethical rule for research. Includes gender , age, jobs, marital status , education, family monthly per family member income, waist / hip ratio, type-2 diabetical, fasting & post-prandial glucose, medical glycosylated haemoglobin HbA1c report (during the final 30 days), name, formulation, strength, antidiabetic drug price, & side effects.

Data analysis

Data obtained from a specific CRF were Microsoft excel & checked not by the interviewers but by the authors. Microsoft analysed the data to find important statistics. Qualitative variables were analyzed statistically, offered as frequencies & percentages.

Cost- effectiveness calculations

Cost effectiveness estimated were done by following method.

Bioavailability: It was identified from the standard pharmacology text book.6

- Tolerability: Percentage adverse drug reactions (ADR) were determined by following formula= (Number of adverse drug reactions/Number of patients on the treatment)×100.
- Tolerability was calculated as= 100-%ADR
- Efficacy: Efficacy estimate were done by subsequent formulas.
    - Fasting blood glucose (FBG) efficacy. (Participants' FBG–130)/1.3
    - Post prandial glucose (PPG) efficacy. (Participants' PPG–180)/1.8
    - Drug efficacy for single patient = (FBG efficacy + PPG efficacy)/2
    - Average efficacy for a treatment = total efficacy for treatment/number of patients on that treatment.
- Safety of administration: For oral drugs was 100%.
- Frequency of administration: ratings were as follows OD=100, BD=50, TID=33.3, QD=25.
- Effectiveness of a treatment option = Sum of all criterion rating,
    - Where (Criterion Rating=Criterion value ×Assigned weight).
    - Weights assigned were based on Abdulganiyu 's earlier analysis.
- Cost effectiveness Analysis (CEA) has following method:
    - Long time management is antidiabetic therapy, but a doctor is seen every 2-3 months to monitor. So for all treatments, the duration of therapy was considered as 3 months for calculations of cost effectiveness.
    - CEA= (Total cost for a treatment option for 3 months/ Effectiveness of the treatment option).
- For and anti-diabetic treatment option prescribed in this report, this has been achieved & compared.
- Sensitivity analysis was conducted in order to determine if decisions changed when particular variable (such as cost and efficacy) were adjusted to a less cost efficient alternative for T2D treatment within a realistic range (10-25%).

RESULTS

Table 1 indicates the participants from Mumbai during study socio-demographic parameters. A total of 152 participants with 76 (50%) males, 76 (50%) females were studied. The mean age was

54±11 years. Marital status, occupation, income and education of the participants is as given in Table 1.

Table 1: Socio-demographic parameters of analysis participants

Parameters (N=152)	Frequency	Percentage (%)
Gender		
Male	76	50
Female	76	50
Religion		
Hindu	152	100
Marital status		
With partner	145	95.4
Single	7	4.6
Occupation		
Employed	51	33.6
Business	40	26.3
Housewife	44	28.9
Retired	17	11.2
Monthly income / person		
Upper high class (≥10,000 INR)	38	25
High class (5000 to 9999 INR)	114	75
Education		
Graduate	93	61.2
Non graduate	59	38.8

Based on waist to hip ratio measurements, central obesity was seen in 33 (43.4%) male and 37 (48.7%) female participants. The glimepiride 33 (40.2 percent), Vildagliptin 15 (18.3 percent), Glimepiride 14 (17.1 percent), Glimepiride+Pioglitazone 12 (14.6 percent) & Repaglinide 8 (9.8 percent) were identified as a total among a total of 82 non-obese people. In 70 obese participants, a maximum of 35 (50 percent) was treated with metformin, accompanied by 31 (44.3 percent) & 4 (5.7 percent) with repaglinide. As given in Table 2, efficiencies alone were higher than Glimepirides (95.6), Gliclazides (88.4), Vildagliptin (87.6) & Repaglinides (73.4) for non-obese participants when their ranking for Glimepiride+Pioglitazone (96.4) was taken into account. The requirements for Glimepiride+metformin were higher in obese participants (90.8) than Metformin (80.9) & Repaglinide (73.4).

Table 2: Efficacy of treatment options for the analysis

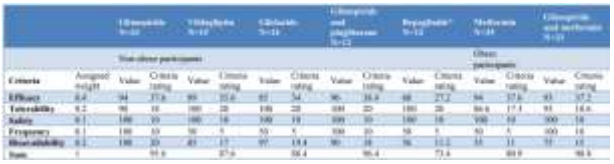
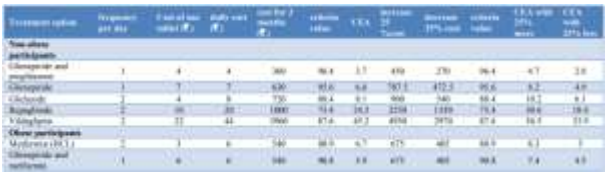


Table 3: Analysis of CEA & sensitivity analysis of treatment options utilized in the research



As shown in Table 3, Glimepiride+Pioglitazone has been less expensively expensively ('3,7) per unit of efficacy followed by Glimepiride ('6,6), Gliclazide ('8,1), Repaglinide ('24,5), & Vildagliptin ('45,2) for the treatment of T2DM in non-obese participants. Metformin cost least ('6.7) per unit of efficacy for T2DM in obese participants, accompanied by Glimepiride+Metformin ('5.9) and Repaglinide ('24.5) for care. Analysis of sensitivity, carried out by assuming 25% cost increase & 25% cost decrease, suggests that the decision is still true, that Glimepiride+Pioglitazone confirms that the non – obese T2DM participants received the cheapest medication, whereas obese T2DM participants received metformin.

DISCUSSION

Glimepiride+pioglitazone (96.4) is more effective than Glimepiride (95.6), Gliclazide (88.5), Vildagliptin (87.6) & Repaglinide (73.4) for non-obese participants. This is in agreement with UKPDS report which established that, although relatively effective in the short term, oral agent monotherapy with sulfonylureas or metformin is insufficient to maintain glycemic control against the relentless background of progressive beta cell failure. Metformin is usually only temporarily supplied with sulfonylurea, & many patients need other therapies. Other options for combination therapy with oral agents have been developed by thiazolidinedionos. In T2D it seems that combining a thiazolidinedion & sulphonylurea is a rational therapeutic strategy as their distinct complementary mechanism to minimise glycemia offers a synergy potential.. The clinical experience found that glimepirides of 33 (40.2%), following Vidagliptin of 15 (18.3%), Gliclazide of 14 (17.1%), Glimepyride of + Pioglitazone of 12 (14.6%) & Repaglinide of 8 (9.8%) were regarded as the highest possible amount of non obese people. This indicates that the theoretical evidence available is distinct from its application in clinical practise.

This is consistent with Kim's research, which demonstrated a higher efficacy of combination therapy with metformin and glemepiride than metformin. The most common oral hypoglycamic agents in the world are Glemepiride and méformin. In most patients with newly-diagnosed type-2 diabetes, metformin increases resistance to insulin & prescribed as the first choice drug. Glimepiride is a sulfonylurea of the third generation that activates the secretion of insulin. Cost effectiveness analysis results were line with the effectiveness of treatments utilized in the existing study, Glimepiride+Pioglitazone cost least (`3.7) per unit of effectiveness in case of non-obese participants. Metformin (`6.7) and Glimepiride+Metformin (`5.9) were similar in terms

of cost per unit of effectiveness in case of obese participants.

CONCLUSION

The findings of this analysis support the reported fact that cost effectiveness analysis could help to make decisions about whether new drugs should be included in a drug formulary list where decisions are made. These decisions are made based on the principle that if a drug is not better than a comparable product, it should not cost more, if it is superior to existing therapies but more expensive (a common situation) and funds are available, any extra expenditure should represent "value for money". The existing results are important because they include a cost effectiveness guideline for institutional care and the advancement of the type method for antidiabetic therapy. This and/or other similar research methodologies may also be used to formulate an institutional care strategy for Antidiabetic Therapy & Hospital Drug Forms focused on cost-effectiveness. In Indian public & private hospitals this pharmaco-economic approach is currently missing. The work provides evidence based information that could be used to change prescription practice- irrational prescription of less cost-effective anti-diabetics over more cost-effective ones, by using the information for educational intervention at prescribers' and managerial levels. The resultant effect will be cost savings in drug therapy.

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